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CHEMOSELECTIVE REACTIONS OF FUNCTIONALIZED PIPERIDINES

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The reduction-oxidation strategy for transformation of a cyano function into a carbomethoxy function was investigated as an alternative to the well-studied hydrolysis routes for viability with alpha-aminonitrile 2. Chemoselectivity problems were minimized when the reduction was effected with diisobutylaluminum hydride under inverse addition conditions.

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PREFACE

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CHEMOSELECTIVE REACTIONS OF FUNCTIONALIZED PIPERIDINES

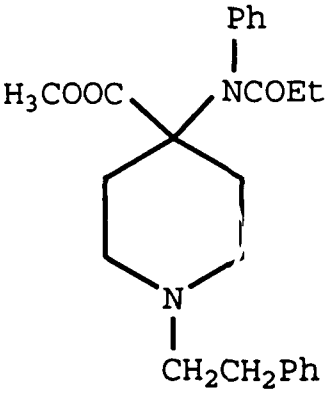
1. INTRODUCTION

Piperidines are an important family of organic compounds due in part to the fact that many of these compounds evoke powerful physiological responses. The substitution pattern of functional groups on the heterocyclic ring is intimately connected to the nature, potency and duration of the response. For example, profound analgesia is produced by administration of certain 4-substituted piperidines (for example, morphine), while a much weaker analgesia is produced by 2-substituted derivatives. It has been established that the reason for this difference is that the former compounds bind to the μ-receptor, while the latter to the κ-receptor.

The isolation of morphine from opium by Sertürner in 1806 marked a major advance in the treatment of pain. With this purified substance in hand, reproducible administration could be accomplished, rather than depending on a qualitative assessment of the potency of a given sample of opium to determine the appropriate dose. In spite of this, morphine is far from an ideal drug. It has many side effects, most importantly respiratory and cardiovascular depression. Accordingly, the search for improved drugs has continued along two general paths. Additional analgesics have been found in natural sources, and ambitious research has been conducted to prepare synthetic compounds. The thrust in the second approach has been to prepare extremely potent compounds with the expectation that they would be extremely selective at low dosage for the μ-receptors, producing the desired analgesia, but would leave unactivated those receptors leading to side effects. The selectivity of drugs for a particular receptor at low concentration may be likened to controlling the volume of noise made around a sleeping tiger. If the desired reaction is to have the tiger twitch his whiskers only, then it is wise to limit the noise level; too high a level will waken the tiger with all the untoward consequences.

In the 1960's 4-anilidopiperidines have been discovered that are more than three orders of magnitude more potent than

morphine.[1] The parent compound in this series, fentanyl, almost 300 times more potent than morphine in animal studies, had minimal cardiovascular depression, leading to its use in open-heart surgical procedures. Respiratory depression persisted with fentanyl, however. This result was nonetheless encouraging, and suggested that the overall strategy was valid. The search for the even more potent analgesics continued.[2,3] We have focussed our attention on improved syntheses of N-[1-(2-phenylethyl)-4-methoxycarbonyl-4-piperidinyl]-N-phenylpropanamide, **1**, "carfentanil," which is one of the most potent of these materials.



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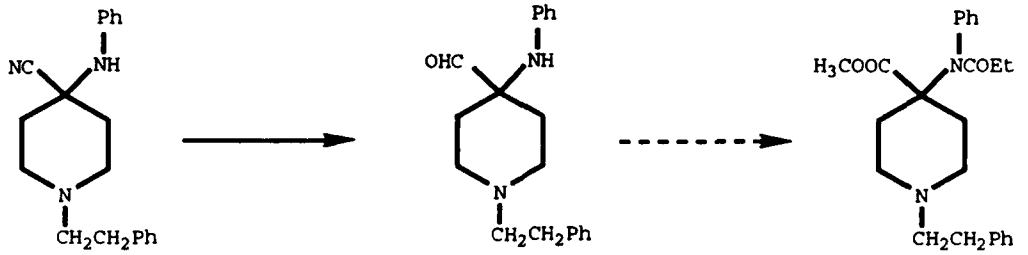
Practical syntheses of **1** began with the α-aminonitrile **2** generated from the reaction of commercially available 1-(2-phenylethyl)-4-piperidone with aniline and KCN. Optimization of conditions for this reaction led to yields of over 90%.[4] While this work was in progress, Feldman[5] reported a route to the 1-benzyl precursor to **1** through a hydantoin intermediate in an overall yield of 26%; Taber[6] developed conditions for conversion of the corresponding carboxamide to this precursor in 61% overall yield.

2. RESULTS AND DISCUSSION

We decided to pursue an entirely different route that would avoid hydrolytic routes and their attendant complication of reversion to the starting ketone. Methods for selective reduction of the nitrile function to a formyl group were explored. It was expected that chemoselective

conditions for conversion of this reactive aldehyde to the carboxyl or methoxycarbonyl fucntions could be found in a straightforward manner (Scheme 1).

Scheme 1

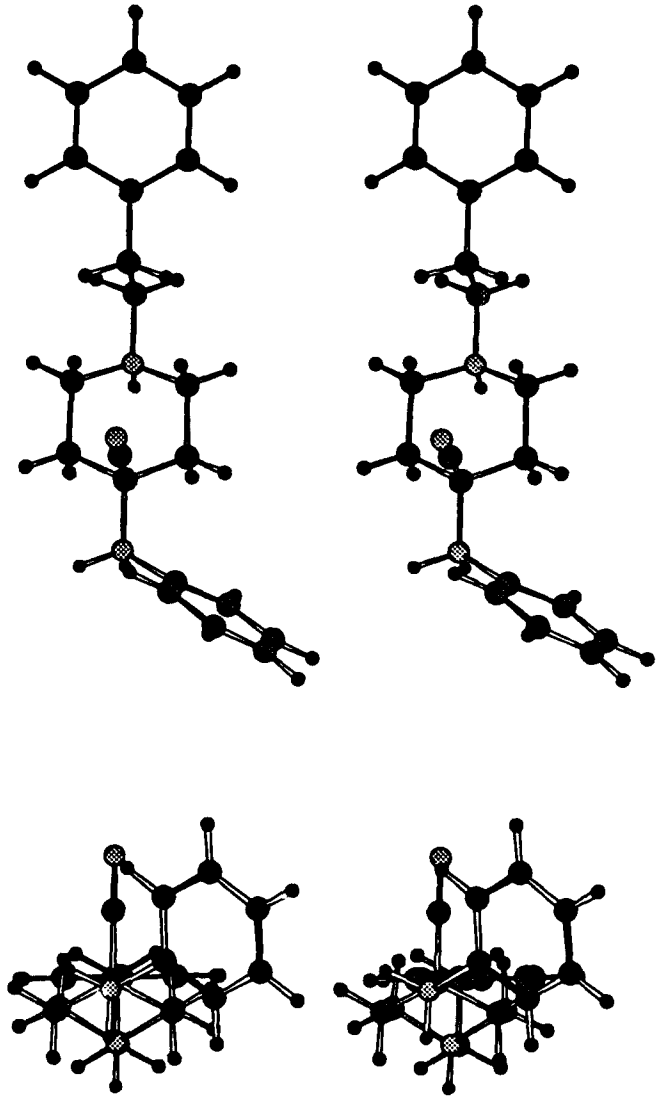


There are many literature methods for conversion of cyano into formyl functions. The requirement is that a two-electron reduction to the imine (hydrolyzed during workup to the aldehyde) occur under conditions such that the product imine is inert. For α-aminonitriles bearing an amino hydrogen, there is an important competing reaction. Reductive decyanation can occur if this proton is removed, and cyanide ion is expelled producing an intermediate imine that is reduced under the reaction conditions. Stereochemical evidence for such a mechanism was obtained in one of our laboratories using the diastereomers of the 3-methyl derivative of **2** and $NaBH_4$, Red-Al, Super-Hydride and L-Selectride.[7]

One approach to avoiding the expulsion of cyanide ion resulting from removal of the anilino proton is to conduct the reduction under acidic conditions. The Stephen reduction using anhydrous tin (II) chloride in the presence of HCl(g) in diethyl ether is such a reaction.[8] This reaction was applied to α-aminonitrile, **2**, without success. Possible reasons for this result are the insolublity of **2** in Et_2O, and poor chemoselectivity. In an environment of excess HCl, the two amino functions, i. e., the heterocyclic nitrogen and the anilino nitrogen, will be protonated before the cyano site. The addition of HCl across the cyano group is required for formation of the putative imidoyl chloride intermediate.[8,9] The geminal location of an anilinium functionality may

present steric (see Fig. 1 for stereoviews from above and from the direction of the N-C_4 bond) and electronic (i.e., the resistance offered by a proton in adding to a doubly positively charged species) challenges to the $SnCl_2$-catalyzed addition of HCl to the nitrile function.

Figure 1. Stereoviews of **2·2HCl**



Successful cont.olled reduction of nitriles to aldehydes using $LiAlH_4$ has been reported.[8] For example, 4-dimethylamino-2,2-diphenylvaleronitrile reacted with 1 equiv. of LAH to provide an 82% yield of 4-(dimethylamino)-2,2-diphenylvaleraldehyde; however, the isomeric 3-(dimethylamino)-2,2-diphenyl-3-methylbutyronitrile gave a yield of only 24% of the corresponding aldehyde.[11] When a solution of **2** was treated with two equivalents of LAH, the starting material was recovered in excellent yield, comprising ca. 95% of the product, along with 1-(2-phenylethyl)-4-phenylaminopiperidine, **4**.

The chemoselective reduction of **2** to the corresponding diaminoaldehyde **3** was accomplished using DIBAL-H (Table 1).

Table 1. Summary of Reaction Conditions for DIBAL-H Reduction of **2**.

Reducing Agent	Reaction Conditions	Hydrolysis and Workup	Yield of 3
$CuBH_4$ (CuCl+$LiBH_4$)	THF, -20°C to R.T. 2.5 hrs	1N HCl, CH_2Cl_2 extraction	no desired product
$CuBH_4$ ($CuBr^1$+$LiBH_4$)	THF, -10°C to R.T., 3 hrs	1N HCl, CH_2Cl_2 extraction	no desired product
$LiAlH_4$	Et_2O, 0°C, 30 min.	1N HCl, CH_2Cl_2 extraction	minor on TLC
DIBAL-H (1.2 eq)	Toluene, -78°C, 2 hrs	Na/K tartrate, CH_2Cl_2 extraction	no reaction
DIBAL-H (2.5 eq)	Toluene, -78°C, 2 hrs	Na/K tartrate, CH_2Cl_2 extraction	minor on TLC
$Li(EtO)_2AlH_2$[2]	Et_2O, 0°C, 2.5 hrs	MeOH, Na-tartrate,CH_2Cl_2 extraction	no reaction
DIBAL-H (2 eq)	50% IPA/MTBE[3], -25°C to rt*	50 % AcOH, CH_2Cl_2 extraction	minor on TLC
DIBAL-H (3 eq)	Toluene, -78°C ,16 hrs	50 % AcOH, CH_2Cl_2 extraction	minor on TLC
DIBAL-H (5 eq)	Toluene, -78°C ,1.5 hrs	MeOH/H_2O, Al_2O_3	6 %
DIBAL-H (4 eq)	Toluene, -78°C ,1.5 hrs	MeOH/H_2O, Al_2O_3	4 %
DIBAL-H (4.3 eq)	Toluene, -78°C to reflux	No Workup	4 %
DIBAL-H (10 eq)	Toluene, -78°C, 3 hrs	MeOH/H_2O, Al_2O_3	4 %
DIBAL-H (5 eq)	THF, -78°C to R.T	MeOH/H_2O, Al_2O_3	17 %
DIBAL-H (2 eq)	THF, -78°C to R.T	MeOH/H_2O, Al_2O_3	6 %
DIBAL-H (3 eq)	THF, -78°C to R.T	MeOH/H_2O, Al_2O_3	6 %
DIBAL-H (5 eq)	THF, -78°C to R.T	MeOH/H_2O, Al_2O_3,scale up	8.7 %
DIBAL-H (5 eq)	THF, -78°C to R.T.	MeOH/H_2O, Al_2O_3	18 %
DIBAL-H (5 eq, precooled)	THF, -78°C to R.T. (LA[4])	MeOH/H_2O, Al_2O_3	18 %
DIBAL-H (5 eq, precooled)	THF, -78°C to R.T. (LA)	MeOH/H_2O, Al_2O_3, scale up	minor on TLC
DIBAL-H (5 eq, precooled)	THF, -78°C to R.T. (LA)	MeOH/H_2O, Al_2O_3, scale up	5 %
DIBAL-H (5 eq, precooled)	THF, 0°C, 3.5 hrs (LA)	MeOH/H_2O, Al_2O_3	18 %
DIBAL-H (5 eq, precooled)	THF, 0°C, 75 min. (LA)	MeOH/H_2O, Al_2O_3,scale up	15 %

1. $CuBr{\cdot}SMe_2$ was used
2. Prepared from $LiAlH_4$ + 2EtOH
3. Methyl t-butyl ether
4. Inverse Addition
*reflux

Other hydrides used in this study, $CuBH_4$, $Li(EtO)_2AlH_2$ and $LiAlH_4$ in Et_2O for short reaction times, were unsatisfactory. The best conditions were the use of 5 equiv of DIBAL-H, THF as solvent and inverse addition. Clearly the need for excess DIBAL-H is due to the fact that there are two Lewis base sites in the molecule that are more reactive than

the cyano function. The Lewis acid center of DIBAL-H complexes with the ring nitrogen electron pair and that of the anilino function before delivery of hydride in the reduction step. Such complexation apparently renders the rate of reduction faster than that of reductive decyanation.

The best yield obtained was 18%, however, it should be emphasized that this is an isolated yield. Additional study of the workup procedure should result in a significant improvement in yield.

3. EXPERIMENTAL METHODS

α-Aminonitrile, **2**, was prepared as described previously.[4] It could be recrystallized to a constant melting point of 121.0 - 121.5° after dissolution in boiling hexane. Alternatively, the crude product could be purified by passing through a short silica gel column, eluting with ethyl acetate/n-hexane, 60/40: v/v, followed by recrystallization from 10% ethyl acetate in n-hexane (v/v). Diisobutylaluminum hydride (DIBAL-H, 1.0 M in hexanes) was purchased from Aldrich Chemical Co., Inc. Tetrahydrofuran (THF) was distilled from benzophenone ketyl under an Ar atmosphere. ^{1}H and ^{13}C NMR spectra were obtained using a Varian XL-400 spectrometer. Chemical shifts are reported for $CDCl_3$ solutions in ppm downfield from the internal standard, tetramethylsilane.

3.1 4-Cyano-4-(phenylamino)-1-(2-phenylethyl)-piperidine (2). ^{1}H NMR 7.31 - 7.18 (m, 7 H); 6.95 - 6.91 (m, 3 H); 3.65 (bs, 1 H); 2.94 - 2.90 (m, 2 H); 2.83 - 2.79 (m, 2 H); 2.69 - 2.65 (m, 2H); 2.56 - 2.50 (m, 2 H); 2.40 - 2.35 (m, 2 H); 1.98 - 1.92 (m, 2 H); mp = 121.0 - 121.5°.

3.2 1-(2-Phenylethyl)-4-formyl-4-phenylaminopiperidine (3). Into a flame-dried 500 mL round-bottomed flask charged with 60 mL of anhydrous THF was introduced 24.6 mL of DIBAL-H (24.6 mmol) via syringe at 0° C under an Ar atmosphere. Into a neighboring 100 mL flame-dried round-bottomed flask was added 1.50 g (4.92 mmol) of **2** dissolved in 90 mL of anhydrous THF. Upon cooling both solutions to 0° C by means of an ice-water bath, the solution of **2** was cannulated to the DIBAL-H solution over a period of 15 min while both solutions were magnetically stirred under Ar. After stirring the

reaction mixture for 75 min at 0° C, the ice bath was removed and replaced with a dry ice/acetone bath to cool the reaction to - 78° C. Hydrolysis was effected by the dropwise addition of 9.0 mL of MeOH, followed by 9.0 mL of water. After stirring for 10 min at - 78° C, the cooling bath was removed, and the reaction mixture allowed to stir for an additional hour, producing a gel-like material. This product was passed through a column containing 25 g of neutral alumina (Woelm Pharma, Super 1), eluting three times with ethyl acetate. Concentration on the rotary evaporator and then at high vaccum (0.05 mm Hg) afforded 1.35 g of crude product. Chromatography on 20 g of silica gel (EM Science, 240 mesh) with n-hexane/ethyl acetate (60/40 : v/v) gave a total yield of 0.541 g of the desired aldehyde **3** and 1-(2-phenylethyl)-4-phenylaminopiperidine (**4**). Recrystallization of **4** from petroleum ether, b. p. = 35 - 70 °C, produced white crystals of m. p. = 92 - 93 ° C. Additional purification by short column chromatography (40 g of silica gel) provided 0.220 g (0.714 mmol, 15 %) of **3**. Recrystallization from n-hexane produced two crops of crystals, totaling 0.103 g: $(m.\ p.)_1$ = 80.5 - 81.0° C: Calcd for $C_{20}H_{24}N_2O \cdot 3/2\ H_2O$: C, 77.21; H, 7.78; N, 9.01. Found: C, 77.11; H, 7.87; N, 9.01. $(m.\ p.)_2$ = 91.0 - 91.5° C: Calcd for $C_{20}H_{24}N_2O \cdot 1/2\ H_2O$: C, 75.67; H, 7.62. Found: C, 75.30; H, 7.78. ^1H NMR 9.63 (s, 1H); 7.30 - 7.13 (m, 7 H); 6.76 (t,J = 7.3 Hz, 1 H); 6.56 (dd, J = 8.6, 0.9 Hz, 2 H); 3.91 (bs, 1 H); 2.82 - 2.77 (m, 2 H); 2.75 - 2.70 (m, 2 H); 2.63 - 2.59 (m, 2 H); 2.44 - 2.40 (m, 2 H); 2.13 - 2.06 (m, 2 H); 1.93 (m, 2 H). ^{13}C NMR 144.7, 140.2, 129.4, 128.7, 128.4, 126.1, 118.8, 114.6 (aromatic carbons), 91.4, 60.3, 48.5, 33.7, 29.6. FTIR ($CHCl_3$) 2928, 1730, 1601, 1503, 1260, 1121 cm^{-1}. EI nominal mass spec (70 eV) m/z 309 (M^+ + 1, 0.4); 308 (M^+, 1.7); 209 (M^+ - CHO, 7.0); 217 (M^+ - CH_2Ph, 100.0). R_f value (ethyl acetate/hexane : 80/20 : v/v): 0.22.

3.3 1-(2-Phenylethyl)-4-phenylaminopiperidine (4). ^1H NMR 7.31 - 7.14 (m, 7 H); 6.70 - 6.67 (m, 1 H); 6.62 - 6.60 (m, 2 H); , 3.53 (bs, 1 H); 3.36 - 3.31 (m, 1 H); 3.00 - 2.97 (m, 2 H); 2.85 - 2.81 (m, 2 H); 2.65 - 2.61 (m, 2 H); 2.26 - 2.20 (m, 2 H); 2.12 - 2.09 (m, 2 H); 1.57 - 1.48 (m, 2 H). m. p. = 92 - 93° C; lit[10] 91 - 93 ° C.

3.4 Reduction of 2 with Lithium Aluminum Hydride (LAH). Into a 10 mL round bottomed flask equipped with a magnetic stirring bar was added 101.6 mg (0.333 mmol) of **2**. The reaction vessel was blanketed with dry nitrogen, and then 5 mL of THF was added, followed by the addition of 7.2 mg

0.76 equiv) of LAH in four portions over a 5 min period. An exothermic reaction occured, as evidenced by some bubbling. The reaction mixture was fitted with a septum, and stirred under a dry N_2 atmosphere for 19 h. The THF was removed on the rotary evaporator, and 1 mL of H_2O, 1 mL of 15% NaOH solution and 3 mL of H_2O were added dropwise and sequentially to the residue. The mixture was then extracted with two 15 mL portions of $CHCl_3$, dried over Na_2SO_4 and concentrated first on the rotary evaporator and then at high vacuum to provide 109.7 mg of product. TLC and spectral analysis established that the product was ca. 95% **2**, the remainder consisting of **4**.

3.5 Reaction of 2 Under Stephen Reduction Conditions. Anydrous $SnCl_2$ was prepared by the portionwise addition of 11.5 g of $SnCl_2 \cdot 2\ H_2O$ to 10.0 mL of magnetically stirred acetic anhydride.[8] The product precipitated from the exothermic reaction mixture and after cooling to room temperature, the liquid was removed by decantation and the precipitate was washed twice with 20 mL portions of anhydrous diethyl ether, and collected by filtration in virtually quantitative yield.

Hydrogen chloride was bubbled for 1-2 min into a 125 mL Erlenmeyer flask containing 255 mg (0.984 mmol) of anydrous $SnCl_2$ suspended in 5 mL of anhydrous diethyl ether. A solution of 100 mg (0.328 mmol) of **2** in 2 mL of $CHCl_3$ was added in one portion to the magnetically stirred reaction flask. After 2 d of stirring, the reaction mixture was washed with 30 mL of $CHCl_3$ and filtered. A gummy material amounting to 0.03 g after drying was removed, leaving 0.14 g of a white solid. The white solid was boiled for 1 h with 0.03 M HCl, and upon cooling, extracted with $CHCl_3$. Concentration of the dried (Na_2SO_4) $CHCl_3$ solution gave 10 mg of residue, which was tentatively identified as unreacted **2** by TLC.

4. CONCLUSIONS

A number of methods for chemoselective transformation of the cyano functionality of **2** into a formyl group have been explored. It was found that the most promising method was reduction using diisobutylaluminum hydride and inverse addition. While the overall *isolated* yield of the reaction is 18%, conditions for the reaction, but not workup were optimized. It is likely that improved workup will result in palpable improvement in yield.

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